

## Intramural papers of the month

By Deacquita Diggs, Gabriel Knudsen, Gwendolyn Louis, and Simone Otto

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### SIRT1 plays a vital role in bile acid absorption and homeostasis

NIEHS researchers and collaborators discovered that Sirtuin 1 (SIRT1), a nicotinamide adenine dinucleotide-dependent protein deacetylase and key regulator of energy balance, is also important for bile acid homeostasis in the intestines. A dysregulation of bile acid homeostasis has been associated with liver damage and a host of other gastrointestinal and metabolic diseases.

Using a genetically modified, tissue-specific SIRT1 knockout mouse model, SIRT1 iKO, researchers found that SIRT1 deficiency in the intestines decreased the transport of bile acids across the ileum, by reducing the signaling of the hepatocyte nuclear factor 1alpha/farnesoid X receptor pathway. These mice also displayed reduced absorption of intestinal bile, increased liver bile acid synthesis, and decreased liver accumulation of bile acids. SIRT1 iKO mice on a high bile acid diet were partially protected from developing liver damage.

The authors suggest that therapeutics that specifically target intestinal SIRT1 could be developed to treat bile acid-related diseases, such as cholestasis, a condition in which the flow of bile from the liver to the duodenum, the first part of the small intestine, is slowed or blocked. **(GL)**

*Citation:* Kazgan N, Metukuri MR, Purushotham A, Lu J, Rao A, Lee S, Pratt-Hyatt M, Lickteig A, Csanaky IL, Zhao Y, Dawson PA, Li X.

(<http://www.ncbi.nlm.nih.gov/pubmed/24389307>)

2013. Intestine-specific deletion of SIRT1 in mice impairs DCoH2-HNF-1alpha-FXR signaling and alters systemic bile acid homeostasis. *Gastroenterology*; doi:10.1053/j.gastro.2013.12.029 [Online 31 December 2013].

### X-ray crystallography reveals previously unknown damage response pathway

Lesions that result from the insertion of RNA into DNA are removed by the protein aprataxin, according to researchers at NIEHS. The scientists named the process RNA-DNA damage response and believe it is responsible for removing many potentially harmful DNA lesions. Mutations in aprataxin, however, impair efficient processing of RNA-DNA damage. The inability to remove RNA-DNA lesions may contribute to ataxia with oculomotor apraxia 1 (AOA1), a heritable cerebellar-wasting condition, as well as other neurodegenerative diseases linked to APTX mutations.

The researchers studied aprataxin and RNA-DNA interactions using X-ray crystallography, coupled to biochemistry and genetics, in yeast. They crystallized human aprataxin mutants in complex with RNA-DNA substrates, to visualize the aprataxin lesion processing reaction in high resolution. They determined that one of the AOA1 linked aprataxin mutations, which differed from the wild-type by only a single amino acid, distorts the RNA-DNA damage recognition pocket in the protein and blocks its ability to efficiently recognize and process RNA-DNA lesions.

This work helped to establish and expand the hypothesis that progressive neurological diseases, such as AOA1, may in part be due to repeated incorporation of ribonucleotides into genomic DNA over many years in quiescent neurons. Aprataxin gene mutations are critical in heritable AOA1-type neurological diseases, and understanding these molecular mechanisms may aid in new therapies for neurological diseases and certain types of cancer. **(GK)**

*Citation:* Tumbale P, Williams JS, Schellenberg MJ, Kunkel TA, Williams RS.

(<http://www.ncbi.nlm.nih.gov/pubmed/24362567>)

2014. Aprataxin resolves adenylated RNA-DNA junctions to maintain genome integrity. *Nature* 506(7486):111-115. [[Story](#)]

### Nicotine enhances neuronal firing in hippocampal cells

NIEHS researchers have elucidated the cellular mechanism by which nicotine has a positive cognitive effect in hippocampal neurons, according to a study in the *Journal of Neuroscience*. The work provides a basis for novel therapeutics for combatting cognitive impairment in disorders such as schizophrenia and Alzheimer's disease.

Specifically studying the synaptic connection between dentate granule cells and the pyramidal cells of the CA3 region of the hippocampus, scientists discovered that activation of presynaptic, but not postsynaptic, alpha7 nicotinic acetylcholine receptors enhances the current in the postsynaptic cell. Scientists used biosensors to confirm the importance of presynaptic activity. Stimulation of presynaptic nicotinic receptors increased the level of calcium generated by action potentials, which, in turn, increased the likelihood of neurotransmitter release onto CA3 pyramidal cells. This stimulation resulted in an increase of the amplitude of the excitatory postsynaptic current. Since the effects of this stimulation persisted for several minutes, they further demonstrated it was accomplished through a mechanism involving the calcium-dependent signaling molecule protein kinase A (PKA).

The connection between dentate granule cells and CA3 neurons controls the neuronal output of the hippocampus. Determining the mechanism by which nicotinic receptors modulate this output improves the understanding of how nicotine affects hippocampal-dependent learning and memory. (SO)

*Citation:* Cheng Q, Yakel JL.

(<http://www.ncbi.nlm.nih.gov/pubmed/24381273>)

2014. Presynaptic alpha7 nicotinic acetylcholine receptors enhance hippocampal mossy fiber glutamatergic transmission via PKA activation. *J Neurosci* 34(1):124-133.

## Identifying respiratory syncytial virus risk using gene markers

NIEHS researchers and collaborators have developed a cell model to investigate genes involved in respiratory syncytial virus (RSV) infection, which is common in infants and children. The model identified candidate genes, and one viral gene in particular, that may be used as a biomarker to validate RSV infections.

Using RSV, the authors infected human lymphoblastoid cell lines (LCLs) from several ethnic groups, including Northern European, African American, and Japanese. They found that RSV infectivity differed among individuals, as well as between the ethnic groups.

In addition, they utilized LCL microarray gene expression data from [HapMap](http://www.genome.gov/10001688),

(<http://www.genome.gov/10001688>)

an international project sponsored by the National Human Genome Research Institute to develop a map of human haplotypes, or genes, that are inherited together, to determine patterns of human DNA variation. Out of the 62 genes that correlated with RSV infection, they found that slight sequence changes, or polymorphisms, in the gene for influenza myxovirus resistance 1 (MX1) were associated with increased expression of RSV in LCLs, and with an increased risk of severe RSV disease in an Argentinian infant cohort. The data suggest MX1 is a susceptibility marker for RSV infection, and the authors' translational approach may be used to predict other genes that confer RSV risk. (DD)

*Citation:* Ciencewicki JM, Wang X, Marzec J, Serra ME, Bell DA, Polack FP, Kleeberger SR.

(<http://www.ncbi.nlm.nih.gov/pubmed/24421397>)

2014. A genetic model of differential susceptibility to human respiratory syncytial virus (RSV) infection. *FASEB J*; doi:10.1096/fj.13-239855 [Online 13 January 2014].

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